Review Article

Perioperative Crystalloid and Colloid Fluid Management in Children: Where Are We and How Did We Get Here?

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It has been more than 50 yr since the landmark article in which Holliday and Segar (Pediatrics 1957;19:823–32) proposed the rate and composition of parenteral maintenance fluids for hospitalized children. Much of our practice of fluid administration in the perioperative period is based on this article. The glucose, electrolyte, and intravascular volume requirements of the pediatric surgical patient may be quite different than the original population described, and consequently, use of traditional hypotonic fluids proposed by Holliday and Segar may cause complications, such as hyperglycemia and hyponatremia, in the postoperative surgical patient. There is significant controversy regarding the choice of isotonic versus hypotonic fluids in the postoperative period. We discuss the origins of perioperative fluid management in children, review the current options for crystalloid fluid management, and present information on colloid use in pediatric patients.
(Anesth Analg 2010;110:375–90)

Fluid management of the pediatric surgical patient presents challenges to both the anesthesia and surgical teams. Typically, the intraoperative management is the responsibility of the anesthesiologist, whereas postoperative orders are written by the surgeons. Both groups rely on formulas and concepts once thought to be certain, but these are presently being examined and challenged, especially in the pediatric literature. The purpose of this review is to outline the history supporting current fluid management strategies and to discuss the effect of recent controversies on future practice decisions.

CRYSTALLOIDS

The "4-2-1 Rule"

Fluid therapy for the ill child was first described in the early 20th century. In 1918, Blackfan and Maxcy[1] reported instilling 0.8% isotonic saline intraperitoneally to successfully treat infants with diarrheal dehydration. Karelitz and Schick, in 1931, administered a continuous IV solution of 5% dextrose combined with either isotonic saline or lactated Ringer's solution (LR) to "detoxify" dehydrated children. Their institution of IV therapy decreased the current mortality rate for childhood dehydration from 63% to 23%.[2] Over the next 30 yr, work by Gamble, Darrow, Crawford, Wallace, and others further defined the nature of the body's extracellular fluid and the rationale for fluid therapy.[3–6]

The 1957 publication by Holliday and Segar[7] first presented a practical method for clinicians to prescribe IV fluids. The suggestions made in this classic article evolved into what is now termed the "4-2-1 rule" for maintenance fluid therapy in children. Based on earlier research done by their peers, the authors described the intimate relationship between physiologic fluid losses and caloric expenditure. The physiologic deficits from urine output and insensible losses of the skin and respiratory tract are equal to approximately 100 mL per 100 kcal metabolized per day. Simply stated, 1 mL of "water" is required for every 1 kcal of energy expended. Based on the computed caloric needs of the average hospitalized patient (Fig. 1), the daily fluid requirements, as proposed by Holliday and Segar, for patients weighing 0–10 kg are 100 mL/kg, for patients 11–20 kg are 1000 mL + 50 mL/kg for each kilogram between 11 and 20 kg, and for patients weighing more than 20 kg are 1500 mL + 20 mL/kg for each kilogram over 20 kg.[7] A weight-based, hourly IV fluid rate, extrapolated from the above formulas, led to what is most frequently used today in pediatric practice, hence the "4-2-1 rule"[8] (Table 1).

In this article, the authors also defined daily maintenance electrolyte requirements. Considering the

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Accepted for publication June 19, 2009.

Reprints will not be available from the author.

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DOI: 10.1213/ANE.0b013e3181b6b3b5

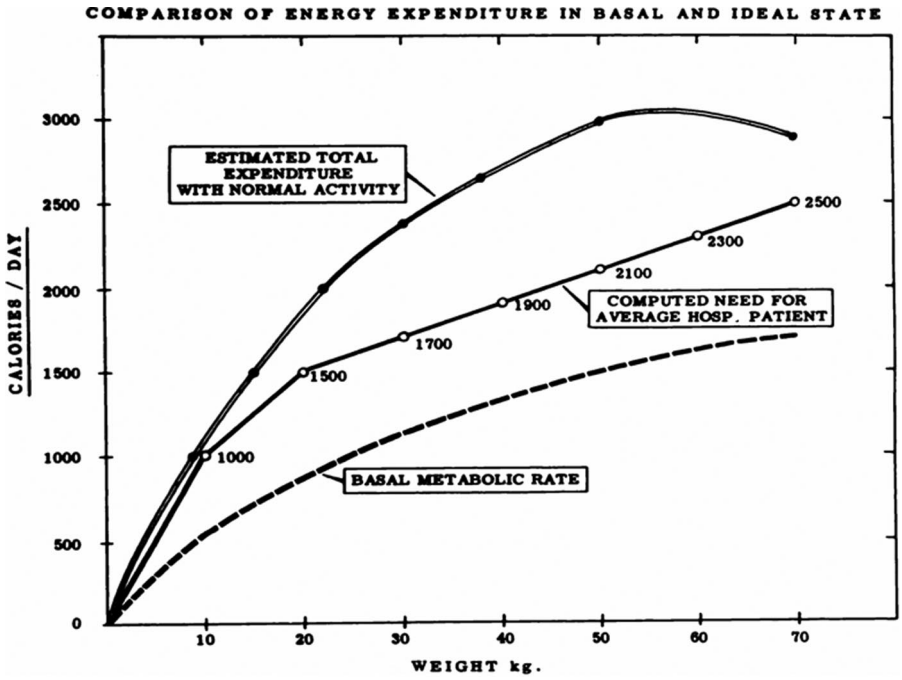

Figure 1. The original graph from the Holliday and Segar article. The upper and lower lines were plotted from previous data measuring caloric needs with normal activity and for basal metabolic rate at 50th percentile weights. The middle line represents computed caloric needs based on the average hospitalized pediatric patient. Under normal conditions, 1 mL of water is required to metabolize 1 kcal, accounting for insensible and urinary losses. Hence, caloric requirements mirror water requirements. (Reproduced from Holliday and Segar[7] with permission.)

Table 1. Daily and Hourly Fluid Requirements Based on Body Weight

Daily fluid requirement	Hourly fluid requirement
3–10 kg: 100 mL/kg	3–10 kg: 4 mL/kg/h
10–20 kg: 1000 mL + 50 mL/kg for each kg from 11 to 20 kg	10–20 kg: 40 mL/h + 2 mL/kg/h for each kg from 11 to 20 kg
>20 kg: 1500 mL + 20 mL/kg for each kg >20 kg	>20 kg: 60 mL/h + 1 mL/kg/h for each kg >20 kg

Adapted from Paut O, Lacroix F, Curr Opin Anaesthesiol, 2006, 19, 268–77.

electrolyte composition of human milk and cow's milk, they recommended 2 mEq · 100 $kcal^{-1} \cdot d^{-1}$ of both potassium and chloride and 3 mEq · 100 $kcal^{-1} \cdot d^{-1}$ of sodium. These electrolyte requirements are theoretically met by the hypotonic maintenance fluid more commonly used in hospitalized children in the United States today, 5% dextrose with 0.2% normal saline. In their conclusions, it was emphasized that "these figures provide only maintenance needs for water. It is beyond the scope of this paper to consider repair of deficits or replacement of continuing abnormal losses of water."[7] Unfortunately, clinicians may often extrapolate the "4-2-1 rule" and the accompanying hypotonic solutions to clinical situations where they may not be appropriate and could, in fact, be harmful.

Perioperative Fluid Requirements

Historically, accepted intraoperative practice has been to administer IV fluids to meet maintenance requirements as well as to replace preoperative deficits and ongoing losses incurred during the surgical procedure. Today, most anesthesiologists have adopted the use of either normal saline or LR for both maintenance and deficit fluid replacement in the operating room setting. There has been little controversy regarding the acceptable maintenance fluid rate as described above. However, considerable debate has occurred regarding the amount of deficit generated by the *nil per os* (NPO) status and the existence of "third space losses."

As a result of the fasting state, children are presumed to develop preoperative fluid deficits secondary to continuing insensible losses and urine output. In 1975, Furman et al.[9] proposed calculating the preoperative deficits by multiplying the hourly rate, as dictated by the Holliday and Segar method, by the number of hours the patient was NPO. They then suggested replacing half of this volume during the first hour of surgery, followed by the other half over the next 2 h. This practice was adopted for many years without questioning its utility. However, in 1986, Berry[10] simplified the method of Furman et al. by delivering a bolus of basic salt solution to otherwise healthy children over the first hour of surgery. Berry concluded that children 3 years and younger should receive 25 mL/kg, whereas children 4 years and older should receive 15 mL/kg.

The methods of both Furman et al. and Berry were developed based on the assumption that patients had been NPO for at least 6 to 8 hours. Fortunately, the debate about the significance of preoperative dehydration secondary to NPO status has become less important due to the liberalization of fasting requirements. In 1999, the American Society of Anesthesiologists

published new fasting guidelines for elective surgery. Current recommendations allow administration of clear liquids up to 2 h before procedures requiring anesthesia.[11] Despite the revised guidelines, patients may still present to the operating room having been NPO for more than the recommended 2 h or having significant deficits related to their disease process. Whereas there are no data to determine the exact amount of fluid deficit that occurs in normal fasting children, strong evidence suggests that healthy adult patients will maintain normal intravascular volumes despite a prolonged fast.[12]

Perioperative Dextrose: The Risks of Hypoglycemia Weighed Against the Risks of Hyperglycemia

In the early 1900s, Karelitz and Schick reported that the addition of glucose to IV fluids in dehydrated children allowed them "to fall into a restful sleep." The authors used a 5% dextrose solution to render the IV fluid isosmolar and to prevent hypoglycemia.[2] Intraoperative dextrose infusion subsequently became common practice in the pediatric population. Although researchers and clinicians acknowledged the deleterious effects of hypoglycemia, Holliday and Segar [7] and Furman et al.[9] warned that the hyperglycemia often occurring subsequent to glucose administration is not without risk.

Hypoglycemia, depending on the severity, can have devastating effects on the central nervous system, especially in neonates. Low blood glucose invokes a stress response and alters cerebral blood flow and metabolism.[13] Permanent neurodevelopmental impairment can result if hypoglycemia goes unrecognized and untreated. In 1967, Anderson et al.[14] first described 6 cases of neonatal hypoglycemia and the disastrous clinical and pathological sequelae associated with prolonged low blood glucose. Animal experiments have further demonstrated that cerebral injury is caused not only by severe prolonged hypoglycemia but also mild hypoglycemia combined with mild hypoxia or ischemia.[15] In a recent study of 35 term neonates with symptomatic hypoglycemia (blood glucose level <45 mg/dL or 2.6 mmol/L), magnetic resonance imaging detected white matter abnormalities in 94%, with severe abnormalities noted in 43% of the studied population. Furthermore, at 18-mo follow-up, 26 of the 35 patients studied continued to exhibit some level of impairment.[16] Hypoglycemia has also been found to be associated with an increase in morbidity and mortality in pediatric intensive care unit (ICU) patients.[17]

In the 1970s, research suggested that fasted children may become hypoglycemic while under anesthesia.[18–21] In 1986, Welborn et al.[22] evaluated preoperative hypoglycemia in 446 children, 1 mo to 6 yr old, scheduled for outpatient minor surgical procedures. There were 2 asymptomatic children with preoperative blood glucose values of <50 mg/dL. Both of these children had fasted in excess of 17 h before presenting to the operating room. The more recent studies on this topic estimate the incidence of preoperative hypoglycemia to be between 0% and 2.5% and usually associated with fast durations from 8 to 19 h, well beyond the current American Society of Anesthesiologists recommended guidelines.[23]

Hyperglycemia has also been recognized as detrimental for the brain. In the presence of ischemia or hypoxia, it is proposed that the impaired metabolism of excess glucose causes an accumulation of lactate, a decrease in intracellular pH, and subsequently severely compromised cellular function that may result in cell death.[13] Hyperglycemia can also induce an osmotic diuresis that may lead to dehydration and electrolyte abnormalities.[23–25] Furthermore, there is evidence in the pediatric literature suggesting that hyperglycemia, especially in the setting of an ischemic or hypoxic event, worsens neurologic outcomes as well as morbidity and mortality statistics in the pediatric population.[17,26–28]

In the 1986 study by Welborn et al., the patients were randomized to intraoperatively receive either LR or 5% dextrose in LR (D5LR). Both the LR and D5LR groups had statistically significant increases in blood glucose. However, the D5LR group had a much larger increase in blood glucose (83 ± 14 mg/dL preoperatively to 244 ± 60 mg/dL postoperatively) than the LR group (85 ± 14 mg/dL preoperatively to 111 ± 22 mg/dL postoperatively).[22]

Based on these results and those of other studies, there is a growing consensus to selectively administer intraoperative dextrose only in those patients at greatest risk for hypoglycemia and, in such situations, to consider the use of fluids with lower dextrose concentrations (e.g., 1% or 2.5%).[23–25,29,30] It should be noted that there are no IV fluids with dextrose concentrations less than 5% commercially available in the United States. The populations at highest risk of hypoglycemia include neonates, children receiving hyperalimentation, and those with endocrinopathies, in whom monitoring blood glucose levels and adjusting the rate of infusion is also recommended.[24,25,30] Routine dextrose administration is no longer advised for otherwise healthy children receiving anesthesia.

Third Space Losses

"Third space losses" refers to the sequestration of fluid to a nonfunctional extracellular space that is beyond osmotic equilibrium with the vascular space.[31,32] In the original study documenting this phenomenon, 13 adults having elective major surgeries (primarily cholecystectomies) were injected with I^{131}-tagged serum albumin, chromate^{51}-tagged red blood cells (RBCs), and sulfur^{35}-tagged sodium sulfate to determine plasma volumes, red cell mass, and extracellular fluid volumes. Additionally, the "trauma" associated with the surgery was rated based on the observed amount of necessary retraction, difficulty in exposure, and depth of anesthesia.[32] The data suggested that

extracellular fluid volume was redistributed or sequestered into areas that no longer communicated with a functional extracellular space and that this correlated with the observed degree of trauma. We have long assumed that the surgical trauma incurred by cell membranes causes hypoxic injury creating a loss of integrity allowing fluids to traverse cell membranes indiscriminately. Isotonic fluids were recommended to replace the losses from the functional extracellular space to the "third space." In pediatrics, it has been proposed that, depending on the nature of the surgical procedure, 1 $mL \cdot kg^{-1} \cdot h^{-1}$ to as much as 15 $mL \cdot kg^{-1} \cdot h^{-1}$ of additional isotonic fluids are necessary to compensate for these continuing losses. In fact, it has been stated that up to 50 $mL \cdot kg^{-1} \cdot h^{-1}$ is required for premature neonates undergoing surgery for necrotizing enterocolitis, a surgery associated with significant trauma and ischemia of the bowel.[25] A recent review of predominantly adult literature concludes that a classic "third space" does not exist.[33] Several studies using multiple blood samples and steady-state tracer kinetics revealed that the functional fluid space is either unchanged or expanded rather than contracted after surgery.[34–36] Substantial amounts of fluid accumulate in the interstitial space secondary to factors including volume overload with crystalloid infusions and iatrogenic deterioration of the vascular barrier.[33]

There is little evidence regarding this topic in pediatric patients. It is possible that our traditional practice of liberal isotonic fluid delivery in major pediatric surgeries may have adverse implications. Several studies in adults demonstrate that, in abdominal surgery, outcomes may be improved by conservative fluid management in the perioperative period.[37–39] Individualized goal-directed fluid management using only the amount of crystalloid and/or colloid necessary to optimize flow-related variables such as stroke volume can alter the incidence of postoperative complications.[40–43] Unfortunately, perioperative studies in pediatric patients using the esophageal Doppler, pulse contour analysis, or mixed venous oxygen saturation to guide and determine optimum fluids are lacking. Instead, we are left to wonder if a smaller amount of crystalloid combined with an appropriate colloid might reduce the amount of tissue edema and improve recovery from surgery previously thought to generate a third space.

COLLOIDS

When determining the particular colloid fluid to administer, the type of fluid deficit (fluid loss or plasma loss) and the effect that these replacement fluids might have on the intravascular volume, coagulation cascade, microcirculation, and any possible allergic reactions must be considered.[44,45] Colloid fluids can be divided into natural protein colloids (albumin) and synthetic colloids (hydroxyethyl starches [HESs], dextrans, and gelatins). These products vary significantly in their chemical, pharmacokinetic, and pharmacodynamic properties, and consequently, these products differ with respect to their impact on hemodynamic variables.

Protein Colloid: Albumin

Albumin occurs naturally and is regarded as the colloid "gold standard." Albumin is derived from pooled human plasma by the Cohn cold ethanol fractionation process: human plasma is heated to 60°C for 10 h and then sterilized by ultrafiltration, thus eliminating the risk of disease transmission.[46] Albumin has a molecular weight (MW) of approximately 69 kDa. In the United States, albumin is produced in concentrations of both 5% and 25%. An albumin 5% solution is osmotically equivalent to an equal volume of plasma, whereas a 25% solution is osmotically equivalent to 5 times its plasma volume. In other words, the administration of 100 mL of 25% albumin will increase the intravascular volume approximately 3–5 times the amount infused. In contrast, the administration of 500 mL of 5% albumin is necessary to increase the intravascular volume by a similar amount of 100 mL of 25% albumin.[47] This intravascular volume expansion occurs because of fluid translocation from the interstitial compartment into the intravascular space. However, in subjects with increased intravascular permeability (e.g., critically ill, sepsis, trauma, and burn), the translocation of fluid from the interstitial compartment to the intravascular compartment may be decreased and colloids may actually leak into the interstitial space, thereby worsening edema by pulling fluid from the intravascular compartment.

Side effects from albumin are rare but have been reported. Although considered to have negligible effects on the coagulation cascade, albumin might still have weak anticoagulation effects through inhibition of platelet aggregation[48] or heparin-like effects on antithrombin III.[49] These effects are thought to be clinically insignificant if volume replacement with albumin is kept below 25% of the patient's blood volume. Tobias et al.,[50] using thromboelastography (TEG®, Haemonetics Corp, Braintree, MA), demonstrated that hemodilution with large amounts of albumin (>25% hemodilution of the blood volume) may produce a hypocoagulable state. Allergic reactions are another possible complication of albumin administration; however, albumin is associated with significantly fewer anaphylactic reactions compared with other colloids.[51]

Albumin's safety has been questioned in 2 separately conducted meta-analyses.[52,53] In the 2004 Saline versus Albumin Fluid Evaluation study, Finfer et al.[54] noted no difference in outcomes between albumin and saline in adults. This 7000-patient multicenter, randomized, double-blind trial, comparing the effects of saline and albumin fluid on the 28-day patient mortality rate, showed no significant difference in mortality (726 deaths in albumin group and 729 deaths in saline group) or secondary end points (length of stay

in the ICU or hospital, days of mechanical ventilation, and days of renal replacement therapy) between the groups. However, there seemed to be an increased mortality in a subset of patients with traumatic brain injury (TBI). A *post hoc* follow-up study was undertaken (Saline versus Albumin Fluid Evaluation–TBI study) that, in fact, substantiated these findings and concluded that critically ill patients with TBI had a higher mortality rate if resuscitated acutely with albumin as opposed to saline.[55]

Pediatric studies are few in number and small in size. In a study of critically ill children with meningococcal disease in the United Kingdom, early aggressive fluid resuscitation with albumin helped to reduce mortality from 50% to <5%.[56,57] Furthermore, in a randomized trial of 30 ventilator-dependent hypoalbuminemic preterm infants, the administration of albumin was associated with a reduction in edema (as judged by weight loss) and inspired oxygen concentration requirements compared with infants who received an equal volume of crystalloid maintenance fluid.[58] In another randomized trial of 30 children younger than 3 yr undergoing cardiopulmonary bypass, the urinary output was 57% lower after intravascular volume expansion with HES 200/0.5 than after albumin administration.[59] In a separate study of children undergoing cardiopulmonary bypass, Riegger et al.[60] compared a pure crystalloid prime with an albumin-added prime solution. The authors noted that patients exposed to the albumin prime had a negative fluid balance and less weight gain after surgery. However, there were no differences between the 2 groups with regard to ICU length of stay, ventilation days, or mortality. In addition, the patients receiving albumin actually had lower hemoglobin levels and higher transfusion requirements.

Albumin has been considered the gold standard for maintenance of colloid osmotic pressure in infants and neonates[61] and continues to be the most frequently used plasma expander in this population.[62] However, the expense and decreased availability of albumin have led some countries to pursue other colloids. The Association of Pediatric Anesthetists of Great Britain and Ireland favor the use of gelatins and the Association of French Speaking Pediatric Anesthetists members from France frequently use hetastarch solutions,[63] whereas in the United States, albumin remains the first choice. There are a multitude of alternative synthetic colloid fluid options accessible in Europe that are not currently available in the United States. Interestingly, in the United States, there is a reduced price differential between albumin and its synthetic alternatives (500 mL of 5% albumin [$82], Hespan (B. Braun Medical Inc. Bethlehem, PA) [$18], Hextend (Hospira Inc. Lake Forest, IL) [$28], Volvulen (Frensenius-Kabi, Bad Homburg, Germany) [$45] LR [$0.77]), whereas in Europe, 500 mL of 5% albumin may cost as much as €150 ($190) and HES fluids may cost €30 ($38). Additionally, the manufacturers of albumin make a concerted monetary effort to encourage the use of albumin.[64] However, data supporting the continued use of albumin for general fluid resuscitation in children are lacking, and in children with TBI, it may actually be harmful. Its utility may exist in specific subgroups such as neonates and patients undergoing cardiac surgery.

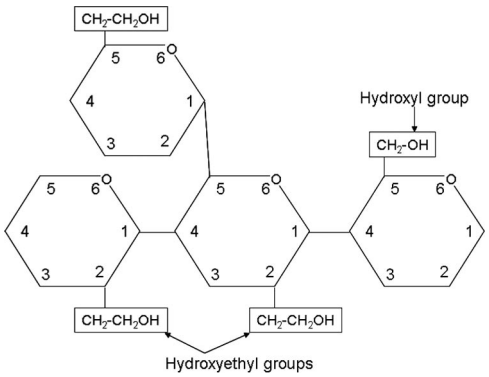

Figure 2. Structure of hydroxyethyl starch (HES). In this molecule, note the 3 hydroxyethyl groups and a total of 4 glucose units giving a high molar substitution of 0.75; all 3 hydroxyethyl groups are on the C_2 carbon giving high C_2:C_6 substitution ratio which leads to prolonged action.

Nonprotein Colloids: HES

HESs are a class of synthetic colloids that are modified natural polysaccharides. Naturally occurring starches are unstable and are rapidly broken down by circulating amylases in the circulation. Substituting hydroxyethyl groups for the naturally occurring hydroxyl groups at carbon positions C_2, C_3, and C_6 results in a more soluble product, resistant to hydrolysis, with subsequent prolonged effectiveness (Fig. 2).

Unlike other colloids, HES colloids are characterized not only by their concentration and weighted average mean MW in kilodalton but also by their molar substitution (MS) and C_2:C_6 ratio (Table 2). Hetastarches are made in concentrations of 3%, 6%, and 10%. Their weighted average mean MW may be divided into low (<70 kDa), medium (130–270 kDa), and high (>450 kDa) brackets. MS is defined as the molar ratio of the total number of hydroxyethyl groups to the total number of glucose units, and these molar ratios may be divided into a low (0.4–0.5) or high (0.62–0.7) molecular ratio. Finally, the C_2:C_6 ratio describes the position of the hydroxyethyl groups on the glucose molecule. As a rule, the solutions with a higher MW and MS ratio have a prolonged volume effect, but are also associated with a greater side effect profile. Initially, HES solutions are broken down rapidly by amylase. The hydroxyethyl groups specific to the C_2 carbon position of the glucose molecule hinder this breakdown and are therefore responsible for prolonging the solution's half-life. Therefore a higher ratio of C_2:C_6 hydroxyethylation substitution results in slower enzymatic degradation and prolonged action without increasing side effects. Hence, the

Table 2. Hydroxyethyl Starch (HES) Solutions Properties and Availability

	HES 450/0.7	HES 670/0.7	HES 130/0.4	HES 70/0.5
Trade name	Hespan®	Hextend®	Voluven®	
Availability	Europe/US	US	Europe/US	Europe
Concentration (%)	6	6	6	6
Volume effect (h)	5–6	5–6	2–3	1–2
Molecular weight (kD)	450	670	130	70
Molar substitution (MS)	0.7	0.75	0.4	0.5
C_2/C_6 ratio	4:1	4:1	9:1	4:1

newest-generation HES fluids are designed with low MW and MS ratios to minimize side effects, as well as a high C_2:C_6 hydroxyethylation ratio to prolong duration of action.

HES solutions expand the plasma volume with effects lasting 2–6 h, depending on the specific characteristics of the HES fluid. In addition to the volume expansion, HES solutions also affect the microcirculation and tissue oxygenation. In a study of adult patients undergoing abdominal surgery, Lang et al.[65] compared a medium MW, low MS HES solution with LR. In this study, the HES solution was noted to have improved tissue oxygenation. As with other colloids, side effects of HES solutions may also include hypocoagulation, renal toxicity, and pruritus.[66,67] These side effects are influenced by the specific characteristics of the HES fluid.[68,69] The older high MW, high MS, first-generation HES solutions (e.g., HES 450/0.7) have more significant hemostatic side effects[66,67] compared with the newer low MW, low MS solutions (e.g., HES 130/0.4).[70,71] The exact mechanism of the hypocoagulable effect associated with the HES solutions is unclear; however, HES seems to interfere with the function of von Willebrand factor, factor VIII, and platelets.[72,73] These hemostatic side effects may be especially concerning in cardiac surgery patients, in whom the use of cardiopulmonary bypass creates further coagulopathies and platelet dysfunction.[45,74,75]

HES solutions may also worsen renal function[75–77] by inducing renal tubular cell swelling and creating a hyperviscous urine. Both tubular cell swelling and hyperviscous urine can cause renal tubular obstruction and medullary ischemia.[78] However, the hyperviscous urine may be preventable, either by prior adequate hydration with crystalloids or by the use of the newer-generation, less-oncotic HES solutions (low MW and MS).[79–81]

Pruritus occurs in 0%–22% of patients exposed to HES solutions and is thought to be caused by the accumulation and storage of the HES solution in the skin. Metze et al.[82] demonstrated the formation of intracytoplasmic vacuoles in the skin after HES fluid administration. The number and size of these vacuoles were noted to be dose dependent. Patients experiencing pruritus consistently showed additional deposits of HES in the small peripheral cutaneous nerves, with symptomatic clinical improvement closely associated with the resolution of these neural vacuoles. These findings led to the conclusion that HES deposits in cutaneous nerves may account for the itching seen after HES infusion.[82] Pruritus may manifest months after the infusion[83,84] and seems to be resistant to current available forms of therapy.[85] The incidence of pruritus seems to be determined by the type of HES solution and the volume administered,[51,86] with less-frequent pruritic symptoms with the new-generation HES solutions.[51,84]

Initially, the only HES solution available in the United States was Hespan® (6% HES 450/0.7 in saline). Hextend® was then introduced (6% HES 670/0.7) and marketed as a balanced colloid solution containing 6% hetastarch, balanced electrolytes, a lactate buffer, and a physiological level of glucose. Hextend seems to be as effective as 6% hetastarch in saline for the treatment of hypovolemia and seems to be a better choice during major surgery than Hespan, with fewer negative effects on the TEG, less blood loss, and less need for calcium supplementation.[87,88]

Voluven® is a 6% HES (130/0.4) solution in 0.9% sodium chloride. It was approved by the Food and Drug Administration in 2007 for the treatment of serious blood volume loss during surgery. Voluven, with its lower MS and MW has relatively little effect on hemostasis. Kozek-Langenecker[89] noted that Voluven use decreased perioperative blood loss and RBC transfusion requirements compared with HES solutions with higher MS ratios. This was further substantiated in a pooled analysis of randomized clinical trials when Voluven 130/0.4 was compared with a second-generation HES 200/0.5 solution.[90] Furthermore, Voluven does not have the negative renal side effects observed with older-generation HES solutions and may, in fact, preserve effective renal plasma flow compared with normal saline.[91] Thus, these newer rapidly degradable HES solutions seem to be a suitable volume expander in the routine perioperative setting because of their adequate volume efficacy and low risk of hemostatic derangements.

Pediatric studies involving synthetic colloids are scant. Paul et al.[92] noted, in a randomized controlled study of children aged 1–38 mo undergoing urologic surgery longer than 2 h duration, that the administration of 20 mL/kg of 6% HES (70/0.5) during the first hour of the procedure resulted in a larger decrease in hemoglobin concentration (more effective plasma expansion) compared with a similar volume of LR. In

addition, Paul et al.[92] noted no differences between the groups with regard to amounts of intraoperative fluid administration, postoperative edema, weight changes, or incidence of pruritus.

Earlier studies in pediatric tumor resection noted that HES was well tolerated and effective in preserving global tissue oxygenation during normovolemic hemodilution in children.[93,94] In a prospective, randomized, double-blind pilot study involving 26 neonates without cardiac, renal, or hemostatic abnormalities undergoing central line placement, the use of 6% HES did not increase creatinine or bleeding when compared with neonates receiving an equal volume of 5% albumin.[95] However, in another small sample size, prospective, randomized, blinded study by the same investigators, no improvement in cardiac output could be shown in 21 hypotensive neonates with low cardiac output states after the administration of HES, isotonic saline, or 5% albumin.[96] Similarly, in a prospective randomized study comparing the new third-generation 6% HES (130/0.4) (Voluven) and 5% albumin, Standl et al.[97] noted no difference in perioperative hemodynamic stability, coagulation variables, blood gas, or other laboratory values in 81 pediatric patients undergoing elective noncardiac surgery. Concerns regarding this study relate to the fact that cardiac surgical patients and preterm patients were not included. Thus, the applicability of these results is limited.

A European prospective, multicenter, observational, postauthorization safety study was designed to evaluate the safety of HES (130/0.42) for perioperative plasma replacement in children. The study was only performed in countries where the use of HES was approved and HES was already indicated for pediatric volume replacement.[98] Three hundred sixteen children, aged 3–12 yr, were infused with a mean volume of 11 ± 4.8 mL/kg of HES (130/0.42). Cardiovascular stability was maintained in all cases. There were no serious adverse drug reactions, such as anaphylaxis, renal failure, or clotting disorder. In this study, only patients with normal renal function and intact coagulation symptoms were investigated, suggesting that although HES may be safe in patients with normal renal and clotting function, further studies are still necessary before presuming safety in patients with renal failure or those at increased risk of bleeding. One potential side effect of HES (130/0.42) noted in this study, however, was a decrease in the anion gap as well as an increase in the chloride concentration. The increase in chloride concentration occurs to maintain electroneutrality because the electroneutral HES replaces the negatively charged plasma proteins, thereby decreasing the amount of unmeasured negative charges.[99] This may be of clinical importance when using anion gap and strong ion difference for acid base interpretation of metabolic disturbances during pediatric surgery. A low anion gap caused by HES infusion could mask a high gap acidosis signifying acute renal failure or sepsis. In addition, the hyperchloremia resulting from HES infusion might have negative effects on arterial blood pressure,[100] renal blood flow,[101] and postoperative nausea and vomiting.[102]

In pediatric cardiac surgery, the data are quite varied. When comparing HES to albumin for postoperative intravascular volume expansion after pediatric cardiopulmonary bypass, there were no differences found in the amount of required replacement fluids or coagulation variables in children receiving 20 mL/kg or less of either colloid replacement therapy. Although an increase in prothrombin time was noted in children who received more than 20 mL/kg of 6% hetastarch, no differences in clinical bleeding or blood product requirement were demonstrated.[103] Similarly, in a randomized trial of 42 patients aged 6 mo to 10 yr, comparing the administration of 10 mL/kg of HES (130/0.4) or fresh frozen plasma (FFP) after cardiopulmonary bypass, Chong Sung et al.[104] reported only a minor effect on coagulation variables. Specifically, there was a prolonged international normalized ratio in the HES group, but no differences were shown between the groups with regard to activated partial thromboplastin time values, transfusion requirements, or blood loss. Haas et al.,[105] in a study measuring coagulation variables with TEG, compared the effects of 15 mL/kg 5% albumin, 4% gelatin, and HES (130/0.4) administered to 42 infants. In this study, there was an increase in activated partial thromboplastin time values with the use of all fluids but a greater reduction of maximal clot firmness (MA value) after gelatin administration when compared with albumin. Median TEG values for both albumin and gelatin, however, remained within the normal range. Patients administered HES, however, exhibited a decrease (below the normal range) both in the speed of clot formation (MA value and α angle) and in fibrinogen/fibrin polymerization (a special additional test that measured clot stability). The authors suggested that this might explain the increase in blood loss after pediatric cardiopulmonary bypass associated with HES use.[105,106] The authors also concluded that from a hemostatic point of view, gelatin was preferable to HES. These hemostatic concerns regarding HES have been further substantiated by a meta-analysis of children and adults receiving HES during cardiac surgery, which showed increased blood loss in those patients receiving HES compared with albumin.[66]

Nonprotein Colloids: Gelatins

Gelatins are polypeptides produced by degradation of bovine collagen. There are currently 3 gelatin products available commercially (crosslinked [Gelofundiol®, Biotest Pharmazeutika, Vienna, Austria], urea crosslinked [Hemacel®, Aventis Pharma, Vienna, Austria], and succinylated gelatin [Gelofusine®, B. Braun, Melsungen, Germany]). None are available in the United States. Gelatin has not been available in

the United States since 1978 because of a high incidence of hypersensitivity reactions with the initial formulations.[107] The MWs of these gelatins are approximately 30–35,000 Da and are lower than the other colloids. It is this lower MW that is responsible for the gelatin's decreased colloid oncotic effects compared with the other colloid fluids. Furthermore, the actual increase in blood volume is less than the infused volume of gelatin because of the rapid but transient passage of gelatins into the interstitial space, rapid glomerular filtration, and gelatin's susceptibility to enzymatic cleavage by proteases. Therefore, repeated infusions are necessary to maintain adequate blood volume. The disadvantage of repeat infusions is balanced by the lack of a gelatin dose limitation. This lack of a dose limitation is distinct from the other nonprotein colloids. There is no accumulation of gelatin in the body, and gelatins have few adverse effects. Other advantages of gelatin include its cost (the least expensive of the synthetic colloids) and its long shelf life.[108] Although initially it was thought that gelatins did not have any negative hemostatic effects, gelatins have been shown to negatively affect TEG values and should be used with caution in patients with bleeding tendencies such as von Willebrand disease.[68,105,109]

The data supporting the use of gelatin in children are limited. A randomized, prospective, double-blind study focused on children with dengue shock syndrome, which is distinguished by hypovolemia secondary to increased vascular permeability. In these children, initial resuscitation was achieved with 1 of 4 fluid regimens (20 mL/kg of dextran, gelatin, LR, or normal saline). All of the children survived, and there was no clear advantage of any of the 4 fluids. However, the LR group was associated with longer recovery times. The authors suggested that the most significant factor determining clinical response was the pulse pressure at presentation and that colloids, which restore the intravascular volume efficiently, might be the better choice of fluids.[110] In a multicenter study, the Northern Neonatal Nursing Initiative Trial Group compared early mortality and morbidity in preterm infants after administration of FFP, gelatin, and glucose. They were unable to show evidence of any adverse short-term outcomes related to gelatin use,[111] and developmental outcome after 2 yr was similar in all 3 groups.[112] However, there was no attempt to evaluate the efficacy of gelatin as an intravascular volume expander in neonates in this study.

Adverse events have been associated with the use of gelatins in infants and older children. In a Cochrane review of early volume expansion in preterm infants (including 7 randomized controlled trials), it was noted that the use of gelatin or no treatment was associated with an increased risk of developing necrotizing enterocolitis, when compared with patients receiving FFP.[113] In a randomized study of children with malaria comparing volume expansion with albumin or gelatin, Akech et al.[114] reported no significant differences regarding success in the treatment of shock or acidosis between the 2 solutions. However, fatal neurological events were more frequent in the gelatin group. In an adult study comparing the use of gelatin or HES for blunt trauma resuscitation, Allison et al.[115] suggested that gelatin was associated with a worse posttrauma capillary leak than HES fluids. Their findings might have implications regarding fluid resuscitation in septic newborns with respect to the severity of their capillary leak syndrome.[116] However, data in animals with regard to capillary leak and septic shock indicate that gelatin and HES actually maintain plasma volume more effectively than albumin.[117]

Nonprotein Colloids: Dextrans

Dextran is a water-soluble glucose polymer (polysaccharide) synthesized by specific bacteria from sucrose. The current formulations available are 10% dextran 40 and 6% dextran 70. Dextran 40 is regarded as a low-MW dextran of approximately 40,000 Da, whereas dextran 70 is a high-MW dextran of approximately 70,000 Da. This leads to a differential excretion of these 2 products by the kidneys, because the renal threshold for these dextrans is approximately 55,000 Da. The result of this differential excretion is that dextran 70 remains in the intravascular space for 5–6 h, whereas dextran 40 remains intravascular for 3–4 h.

Although these dextrans have excellent colloid oncotic powers, they probably should not be used because of their negative coagulation effects and high anaphylactic potential. Their negative coagulation effects are well documented and lead to an increased bleeding tendency.[68] Dextran not only induces a dose-dependent von Willebrand–type syndrome but also enhances fibrinolysis. This fibrinolytic phenomenon is worse with the high-MW dextrans. Furthermore, dextran use has been associated with acute renal failure in patients with acute ischemic strokes.[118] The anaphylactic/anaphylactoid reactions are the result of dextran reactive antibodies, which trigger the release of vasoactive mediators. The current suggestion is to limit the use of dextrans to 1500 mL in an adult or 20 mL/kg in a child per day. It has also been suggested that patients should be pretreated with a hapten inhibition prior to the infusion of a dextran to decrease the incidence of allergic reactions.[119]

HYPERTONIC SALINE

Hypertonic saline solutions have been used in the treatment of refractory hypovolemic shock because of their ability to rapidly mobilize fluid into the intravascular space and thus expand the plasma volume. They have been shown to improve organ blood flow and microcirculation and may even have positive inotropic effects. These solutions are only given in small amounts (4 mL/kg) because of their hypertonicity, but are able to improve preload and thereby cardiac output.[120,121]

The greatest concern with hypertonic saline solutions is their short duration of action. There has been an interest in combining these solutions with colloid solutions, such as HES and dextran, to prolong their positive intravascular effects. These combinations seem to have a beneficial effect and may lead to an improved survival rate in adult patients after trauma compared with the hypertonic saline alone.[122] However, these results have been questioned in a meta-analysis in which patients receiving hypertonic solutions were not shown to have any better outcomes than the patients receiving crystalloids.[123]

Hypertonic saline solutions have, however, been shown to be beneficial in the treatment of TBI by reducing cerebral edema and subsequently decreasing high intracranial pressure.[124–126] Because the blood-brain barrier has a low permeability for sodium, it is thought that the hypertonic saline creates an osmotic gradient to decrease cerebral edema and has a reflection coefficient even better than mannitol. Hypertonic saline may improve brain cell function by reestablishing electrochemical gradients that restore normal resting membrane potential, as well as modulating the inflammatory response, thereby helping to maintain the integrity of the blood-brain barrier and prevent brain cell death.[127–130] In 2 separate studies of children with TBI, hypertonic saline was shown to increase cerebral perfusion pressure in the 3 days after head trauma, when compared with LR.[131,132]

In pediatric burn patients, there seems to be evidence in favor of a combined hypertonic/hyperosmotic solution. In an experimental animal study involving burned pigs, small volumes of hypertonic saline combined with 6% dextran 70 improved heart contractility, reduced cardiac myocyte damage, and reduced total fluid volume compared with LR alone.[133] In a study of burned patients, Murphy et al.[134] noted that a combination of hypertonic saline/dextran 70 solution had no deleterious hemodynamic or metabolic side effects compared with standard LR resuscitation.

There are a number of potential concerns regarding the use of hypertonic saline. There is the theoretical possibility of the development of osmotic demyelination syndrome, rebound increases in intracranial pressure, and acute renal failure from an increase in serum osmolarity.[135] However, in a retrospective chart review by Peterson et al.,[125] no children developed renal failure after the use of hypertonic saline. Hyperkalemia and a nonanion gap metabolic acidosis were common electrolyte abnormalities associated with its use. However, both are easily managed and are not clinically relevant if the serum sodium is kept below 155 mmol/L.

CONTROVERSIES

Crystalloid Versus Colloids

Despite the recognition and focus on the importance of both colloid and crystalloid solutions, there is still a dearth of evidence supporting any particular method of volume expansion in the pediatric population.[136] The International Guidelines 2000 Conference for Neonatal Resuscitation recommended that emergency volume expansion should be accomplished with either isotonic crystalloid solution or O-negative RBCs.[137] A more recent clinical practice guideline from the Dutch Pediatric Society concluded that because of the limited number and quality of available pediatric research studies, recommendations for volume expansion should be made based on the solution's side effects, mechanisms of action, and cost. Thus, isotonic saline was recommended as safe, effective, and 100 times less expensive than albumin.[63]

In the most recent Cochrane database review of colloids versus crystalloids for fluid resuscitation in critically ill adult patients (2007), the authors concluded that there is no evidence to support the use of colloids over crystalloids in the resuscitation of patients with burns, trauma, or after surgery, because they are significantly more expensive and not associated with improved survival.[138] In a letter to the editor, Drs. Jacob and Chappell suggested that patients who do not have substantial blood losses should not generally require the substitution of colloid for crystalloids in their fluid management. Rather, patients with continuing urinary output and insensible losses, representing colloid-free losses, primarily require crystalloid fluid replacement.[139] A further meta-analysis analyzing the different colloid solutions available for fluid resuscitation concluded that when measuring mortality, blood administration, and the incidence of allergic reactions, there was no evidence to suggest that one colloid solution is more effective or safer than another.[140]

There is a tremendous need for well-controlled studies in all pediatric patients that adequately assess the various types of fluid regimens with clearly defined end points. Unitil such studies exist, we continue to extrapolate from adult studies and use a combination of crystalloid and colloids to achieve the desired outcomes.

Postoperative Hyponatremia

In 1983, a study of children undergoing scoliosis surgery demonstrated that hyponatremia developed when hypotonic IV fluids were used postoperatively.[141] In 1986, a report was published of 15 previously healthy women who developed severe postoperative hyponatremia, which resulted in neurologic devastation or death.[142] Six years later, similar catastrophic results were reported in hospitalized children, many of whom were recovering from surgery. The hyponatremia (mean 115 mmol/L) was primarily caused by extrarenal loss of electrolytes, in the presence of increased antidiuretic hormone (ADH) activity, followed by the administration of hypotonic fluids.[143]

Hyponatremia produces osmotic movement of free water across cell membranes from the extracellular to

Table 3. Clinical Settings Associated with Increased Antidiuretic Hormone Production

Hemodynamic stimuli		Nonhemodynamic stimuli	
Hypovolemia	Vomiting, diarrhea, diuretics, diuretics, renal salt wasting, hypoaldosteronism	**CNS disturbances**	Meningitis, encephalitis, stroke brain abscess, head injury, hypoxic brain injury
		Pulmonary diseases	Pneumonia, asthma, tuberculosis, empyema, chronic obstructive pulmonary disease, bronchiolitis, acute respiratory failure
Hypervolemia	Nephrosis, cirrhosis, congestive heart failure, hypoalbuminemia	**Cancers**	Lung, brain, CNS, head, neck, breast, gastrointestinal tract, genitourinary tract, leukemia, lymphoma, thymoma, and melanoma
Hypotension		**Medications**	Cyclophosphamide, vincristine, morphine, selective serotonin reuptake inhibitors, carbamazepime
		Other	Nausea, emesis, pain, stress, postoperative state, cortisol deficiency

CNS = central nervous system.

the intracellular compartments, and the brain is the most seriously affected organ. Estrogens seem to impair the ability of the brain to adapt to hyponatremia. In a review of the adult literature, Arieff[144] reported that women are much more likely to experience permanent neurologic sequelae or even death secondary to hyponatremia. Additionally, menstruant women seem to be at an even greater risk. Ayus et al.[145] reviewed 65 cases of postoperative hyponatremia in adults and found that of the 40 women and 25 men, there were 34 cases of permanent brain damage: 33 of these were women (97%) and 25 were menstruant. The brain Na-K ATPase system, which helps the brain adapt to lower serum concentrations of sodium, is impaired by vasopressin plus estrogen but is stimulated by testosterone.[144] Female rats given vasopressin plus estrogen have greatly reduced cerebral perfusion compared with male rats.[146]

Postmenarchal girls may be at a higher risk of complications than their male counterparts because of these gender differences. In prepubescent children, there are no gender differentials. Rather, all children, regardless of gender, are more prone to cerebral edema than adults. This results from differences in the ratio of intracranial capacity to brain size, cerebrospinal fluid volume, and brain water and electrolyte content. The brain of a child grows rapidly, achieving adult size by age 6 yr, whereas the skull continues to grow until age 16 yr. The volume of cerebral spinal fluid buffers brain expansion, but this is relatively smaller in children than adults. The brain intracellular concentration of sodium is about 27% higher in children than adults.[143] Early in hyponatremia, the brain responds by transporting intracellular sodium to the extracellular environment using the Na^+-K^+ ATPase mechanism.[147] This enzyme activity is decreased in prepubertal animal models.[148] Newborn puppies with hyponatremia are unable to extrude cations from brain cells.[149] The inability of the pediatric brain to adapt to excess free water, along with the high brain-to-skull ratio, help to explain the relatively rapid cerebral edema seen with hyponatremia in pediatric patients.

Another factor that may contribute to a poor outcome in children with hyponatremia is the lack of timely treatment resulting from a low index of suspicion. The early symptoms of lethargy, headache, nausea, and vomiting are common occurrences in many disease states and are often seen in the postoperative period. In children, a respiratory arrest may be the event that triggers identification and subsequent treatment of the electrolyte imbalance. In a series of 16 hospitalized children with symptomatic hyponatremia, all had a respiratory arrest after a mean of 37 h from the start of IV fluid administration, although other milder symptoms were present earlier.[134] Unfortunately, in this series, 10 patients died, 5 survived in a vegetative state, and 1 survived with neurologic deficits. The single patient who survived with moderate deficits was treated within 10 min of the respiratory arrest; therapy was delayed or absent in the others.

The ubiquity of increased ADH, the propensity of the medical community to prescribe hypotonic IV fluids to children, and the lack of routine electrolyte monitoring create the potential for frequent occurrences of hyponatremia. ADH release is associated with many clinical scenarios, resulting from both hemodynamic and nonhemodynamic stimuli (Table 3).[150] The pediatric surgical patient is certainly at risk for increased ADH, given the pain, stress, narcotics, hypovolemia, and/or hemorrhage associated with the postoperative period. Moreover, recent surveys demonstrate that it is common practice to administer hypotonic fluids postoperatively in children.[151–153] Additionally, routine electrolyte monitoring is often not performed unless clinically indicated. Therefore, the true incidence of hyponatremia in these patients is not known but may be much higher than suspected. In a meta-analysis comparing hypotonic versus isotonic fluids in all hospitalized children, the odds of developing hyponatremia after the administration of hypotonic solutions was 17 times greater than with isotonic fluids.[154]

For several years, the general pediatric community has been intensely debating the wisdom of continuing routine hypotonic maintenance IV fluid therapy in

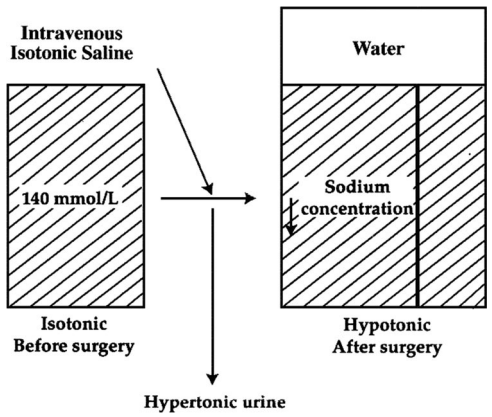

Figure 3. The desalination process. Hatching represents isotonic saline in the extracellular fluid. The rectangle on the left represents the preoperative setting with a normal serum sodium. The rectangle on the right represents the postoperative state. The extracellular space is expanded by isotonic solutions, but the loss of hypertonic urine and retention of free water caused by antidiuretic hormone creates a net increase in hypotonic fluids. This process leads to postoperative hyponatremia. (Reproduced from Steele et al.[164] with permission.)

hospitalized children. Proponents of maintaining the hypotonic requirements outlined by Holliday and Segar argue that extracellular deficits should be replaced first with isotonic fluids, followed by only the amount of fluid and electrolytes required to replace insensible losses and urine output.[155–159] Recognizing that increased ADH levels may affect urine output, decreased volumes are recommended. On the other hand, those who favor using isotonic fluids recognize the potential for iatrogenic hyponatremia and wish to minimize this risk, albeit at the expense of a precise replacement of exact sodium and free water requirements.[160–163] In postsurgical patients, the concern over ADH release causing decreased urine output is confounded by the possibility of volume depletion caused by blood loss or other fluid shifts. The natural inclination when faced with decreased urine output in this scenario is typically to give more volume, not less. The risk of hyponatremia, when faced with oliguria, could be lessened with isotonic fluids regardless of the volume status.

There are at least 2 potential problems when using only isotonic fluids to avoid hyponatremia. The first of these, described only in the adult population, is the phenomenon of desalination. In a study of 22 young women having gynecologic surgery with minimal blood loss, it was described that plasma sodium concentrations decreased an average of 4.2 mmol/L after the administration of large volumes of isotonic fluids.[164] The large volume of fluid administered resulted in hypertonic urine, likely secondary to ADH release both intraoperatively and postoperatively. Researchers proposed that when the extracellular space expands with isotonic fluids, the urinary excretion of a hypertonic solution leaves excess electrolyte-free water leading to hyponatremia and subsequent intracellular swelling (Fig. 3). This process is known as desalination and may be the etiology of the slight hyponatremia reported in some children receiving isotonic fluids.[141,165–168] Although the potential for significant hyponatremia is lower with isotonic fluids than with hypotonic fluids, large volumes of any IV solution, which may collect in the extracellular space, can increase the risk for low serum sodium.

Second, there is a concern that patients who are given isotonic fluids may develop hypernatremia.[158] In a retrospective study of postoperative surgical ICU patients, 11 of 29 patients who received isotonic fluids had at least 1 measurement of sodium larger than 145 mmol/L, compared with 0 of 116 who received hypotonic fluids; no values were considered dangerously increased.[165] The authors also found that 15 of 116 patients receiving hypotonic fluids had moderate or severe hyponatremia in addition to 1 of 29 patients in the isotonic fluid group. In a study of 12 posterior spine fusion patients randomized to isotonic or hypotonic fluids at a rate of 1.5 $mL \cdot kg^{-1} \cdot h^{-1}$, 4 of 7 patients in the hypotonic group had a sodium <130 mEq/mL postoperatively.[166] The control group did not exhibit hypernatremia; rather, there was a small decrease in serum sodium. Hypernatremia was also not observed in 122 primarily postoperative surgical ICU patients randomized to receive either hypotonic or isotonic fluids.[167] At 24 h, the incidence of hyponatremia was 20.6% in the hypotonic fluid group compared with 5.1% in the isotonic fluid group. This finding was replicated by Yung and Keley[168] in their study of both medical and surgical ICU patients who were randomized to 0.9% saline or 4% dextrose with 0.18% saline. Hypotonic fluids were associated with a decrease in serum sodium, with surgical patients experiencing the greatest decrease; no patient was found to have hypernatremia.

This debate regarding hypotonic fluids became the focus of a national inquiry in Great Britain after the deaths of 4 children who became profoundly hyponatremic after receiving hypotonic fluids while hospitalized. In 2007, The National Patient Safety Agency of the United Kingdom issued an alert recommending the removal of 4% dextrose with 0.18% saline from general use in children.[169] The preferred fluids for maintenance therapy are either 0.45% saline with dextrose or isotonic fluids. Additionally, they recommended measuring plasma sodium, potassium, and urea and/or creatinine at baseline and at least once daily in any child who receives IV fluids.

In most countries, there is neither consensus nor mandate about the composition of maintenance fluids in children despite the continuing controversy in the literature. An editorial in a specialty anesthesia journal highlighted the issue and proposed the creation of a new IV solution with a fraction of the glucose and a higher concentration of sodium in comparison to currently available solutions.[29] No such commercial solution is available in the United States. A review of the presently marketed IV solutions demonstrates that

Table 4. Composition of Frequently Used IV Fluids in the United States

Fluid	Glucose (g/100 mL)	Na^+ (mEq/L)	K^+ (mEq/L)	Cl^- (mEq/L)	HCO_3^- (mEq/L)	Ca^{2+} (mEq/L)	mOsm/L	Tonicity[a]
Lactated Ringer's		130	4	109	28	3	273	Hypotonic (slightly)
Normal saline (NS)		154		154			308	Isotonic
D_5W	5						252	Hypotonic
$D_{10}W$	10						505	Hypotonic
D_5 ¼ NS	5	34		34			329	Hypotonic
D_5 ½ NS	5	77		77			154	Hypotonic

[a] With respect to intravascular fluid composition.

Adapted from Kuster JW, Rau RE, eds., John Hopkins: the Harriet Lane handbook, 2008, 18th ed., Elsevier Mosby.

most are hypotonic (Table 4).[170] A 2007 edition of a pediatric textbook has acknowledged the potential for hyponatremia in the postoperative period and advises this generation of pediatricians to expect the administration of isotonic fluids intraoperatively and also immediately postoperatively, albeit at two-thirds of the calculated maintenance rate in the recovery room. It further suggests that subsequent maintenance fluids should contain 0.45% saline in the absence of a specific indication for 0.25% saline. Most importantly, this text stresses the importance of daily electrolyte measurements, regardless of the type of IV solution chosen.[171] This is an important advance in the care of postoperative pediatric patients. Education of all who care for children in the perioperative period about the current recommendations will reduce the potential complications associated with parenteral IV fluids.

CONCLUSIONS

The classic article of Holliday and Segar promoting hypotonic maintenance fluids for hospitalized children provides a solid basis for physiologic management of children's needs relating to insensible losses and urine output. To maintain homeostasis in the intraoperative period, crystalloid fluids should be isotonic in composition. Routine intraoperative dextrose administration is no longer necessary, but high-risk populations such as neonates do require dextrose infusions and monitoring of serum glucose levels. More studies are necessary in the pediatric population to define optimal amounts of fluids to maintain the intravascular space, especially during major surgical procedures. Rather than extrapolating adult and animal data to a susceptible population, research should be directed toward safety and outcomes of synthetic colloid use in children. We should ultimately change our approach to major intraoperative fluid shifts by a rational, monitored, goal-directed combination of both crystalloid and colloid therapy, similar to that occurring in adult surgical patients.[33]

Although no consensus has been reached on postoperative fluid management, recognition of the potential problems associated with "routine" hypotonic solutions is the first step. Other countries have addressed the issue in a decisive way by mandating a change in IV fluids to reduce the occurrence of severe hyponatremia. At the very least, we should change our practice of using D_5 0.2 normal saline and educate others (surgeons and pediatricians) who are responsible for the care of the postoperative pediatric surgical patient.

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Water Water Everywhere: Standardizing Postoperative Fluid Therapy with 0.9% Normal Saline

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In this issue of the journal, Bailey et al.[1] review the pediatric perspectives on crystalloids and colloids. Although the merits of each solution have been continually debated over the years, the choice of the proper postoperative crystalloid solution has become clear.

Patient safety is one of the nation's most pressing health care challenges. There have recently been increased efforts to standardize perioperative care to prevent postoperative complications and deaths. To this end, the World Health Organization has published a surgical safety checklist,[2] which in a prospective study was demonstrated to reduce hospital mortality by almost 50%.[3] One aspect that was not addressed was standardizing postoperative fluid therapy. Hyponatremic encephalopathy is a serious but underappreciated complication of surgery. There have been numerous reports of death or permanent neurologic injury from hyponatremic encephalopathy in otherwise healthy children and adults after common surgical procedures.[4–7] With >200 million surgical procedures performed annually worldwide,[8] we project the morbidity rate for postoperative hyponatremic encephalopathy to be >200,000 cases annually, based on previous projections done in the United States.[5] The primary reason for this complication is the routine administration of hypotonic fluids in the postoperative period and the failure to recognize and treat hyponatremic encephalopathy when it develops. There is good reason to believe that the complication of postoperative hyponatremic encephalopathy could be virtually eliminated by a policy of administering 0.9% sodium chloride (NaCl) postoperatively when parenteral fluids are needed. In 2003,[9] we proposed that 0.9% NaCl be administered for the prevention of hospital-acquired hyponatremia in high-risk pediatric patients, in particular postoperative patients, and we have since extended these recommendations to include adults.[9,10] This generated a significant amount of controversy.[11,12] Since that time, data have emerged from prospective studies in children to show that 0.9% NaCl effectively prevents hyponatremia, whereas hypotonic fluids lead to hyponatremia.[13–15]

Hospital-acquired hyponatremia (Na <135 mEq/L) primarily results from 2 factors in conjunction: (a) an impaired ability to excrete free water because of arginine vasopressin (AVP) excess, and (b) the administration of hypotonic fluids.[12,16] Postoperative patients are at high risk for developing hyponatremia because they have multiple stimuli for AVP production including pain, stress, nausea and vomiting, positive pressure ventilation, the administration of narcotics, and intravascular volume depletion. The combination of these factors places virtually all postoperative patients at risk for developing hyponatremia.

Hyponatremia is not an inevitable consequence of AVP excess. For hyponatremia to develop, there must also be a source of free water. The majority of the morbidity and mortality from postoperative hyponatremic encephalopathy has occurred in patients receiving hypotonic IV fluids.[6,7] Despite the recognition of this serious complication, recent consensus guidelines in the United Kingdom continue to recommend hypotonic fluids in the postoperative period.[17,18] It must be realized that any fluid that has a tonicity, sodium plus potassium, less than that of the aqueous

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Accepted for publication November 4, 2009.

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DOI: 10.1213/ANE.0b013e3181c98131

phase of plasma water (154 mEq/L), is a hypotonic fluid and is capable of producing hyponatremia. Even though a normal plasma sodium is 140 mEq/L, plasma is 7% anhydrous, which makes the sodium concentration in the aqueous phase of plasma water approximately 150 mEq/L. Therefore, 0.45% NaCl (Na 77 mEq/L) and lactated Ringer solution (Na 130 mEq/L) are hypotonic in relation to the plasma sodium and can produce hyponatremia. In theory, even 0.9% NaCl can result in hyponatremia, in the presence of AVP excess where the urine osmolality is >500 mOsm/kg. This is of particular concern in patients with central nervous system (CNS) injury, in whom AVP levels and urine osmolality can be extremely elevated, and even a small decrease in serum sodium can contribute to neurologic deterioration and mildly hyponatremic values.[10,19] To the best of our knowledge, there is not a single report in the literature of a neurologic complication related to the use of 0.9% NaCl in a patient without underlying CNS disease.

Three recent prospective randomized studies in almost 300 postoperative children have confirmed that 0.9% NaCl effectively prevents the development of postoperative hyponatremia and that hypotonic fluids consistently produce a decrease in serum sodium.[13–15] Two of these studies found that the development of hyponatremia was unrelated to the rate of fluid administration but was primarily related to the sodium concentration of the IV fluid.[14,15] Hypotonic fluids produced a decrease in serum sodium even when administered at between 50% and 66% of standard maintenance therapy. The development of hypernatremia was not a significant complication, even in patients receiving normal saline who were restricted to 50% of standard maintenance therapy.[14]

There is no rationale for administering hypotonic fluids in the postoperative setting. Concerns about development of excessive intravascular volume, hypernatremia, hyponatremia from desalinization, or acidosis from administration of 0.9% NaCl, are unfounded. In general, the administration of 0.9% NaCl will produce neither excessive intravascular volume nor hypernatremia, nor will it worsen hyponatremia. When normal saline is administered in the presence of AVP excess, as is seen in the syndrome of inappropriate antidiuretic hormone secretion, the body will preserve extracellular volume at the expense of serum osmolality by excreting a hypertonic urine.[20,21] This physiologic natriuresis will drive the urine output to prevent excessive intravascular volume and will also result in the renal generation of free water, which will prevent the development of hypernatremia.[22,23] It is a misconception that 0.9% NaCl in and of itself will contribute to the development of hyponatremia by inducing a desalinization process, as is often quoted.[24] The renal generation of free water and excretion of a hypertonic urine is a well-known physiologic phenomenon that occurs when IV fluids are administered in the presence of euvolemic states of AVP excess.[25] In the absence of AVP excess, a so-called desalinization will not occur. 0.9% NaCl is also no more likely to produce acidosis than any other commercially available NaCl solution. All commercially available NaCl-containing solutions, including 0.9%, 0.45%, and 0.2% NaCl, are acidic with a pH of approximately 5. This is not attributable to the chloride content in the solution, because the pH of 0.9% NaCl in a glass bottle is 7, but is rather attributable to a chemical reaction between the solution and the IV fluid bag. The majority of IV fluids bags are made from a derivative of polyvinyl chloride and are permeable to carbon dioxide; therefore, no commercially available IV fluid contains sodium bicarbonate because the bicarbonate would dissipate out in the form of carbon dioxide. If large volumes of 0.9% NaCl are administered rapidly, as can occur intraoperatively, a mild dilutional acidosis can occur, but this should not develop at standard maintenance rates postoperatively. Lactated Ringer solution does have an advantage over 0.9% NaCl, because it contains lactate, which can be converted to bicarbonate by the body, but unfortunately it is slightly hypotonic in relation to the plasma and can produce a decrease in serum sodium.[7] Lactated Ringer solution would be more suitable for the perioperative setting if the manufacturers would increase the sodium concentration to 150 mEq/L.

No single IV fluid can be used safely in all situations. Extracellular volume overload could develop if excessive amounts of 0.9% NaCl were administered in the presence of significant renal impairment or congestive heart failure. Similarly, 0.9% NaCl could result in hypernatremia if administered to a patient with renal or extrarenal free water losses as is seen with nephrogenic diabetes insipidus or high nasogastric output. Thus, we have recommended that hypotonic fluids be restricted in their use to patients with either hypernatremia (Na >145 mEq/L) or ongoing urinary or extrarenal free water losses and that patients at risk for extracellular volume overload have their volume of fluid restricted.

Postoperative hyponatremic encephalopathy can be difficult to diagnose because the presenting features are nonspecific and can be confused with other conditions. Headache, nausea, and vomiting are the most universal features of hyponatremic encephalopathy but are also common symptoms of other postoperative conditions.[16] An often overlooked clinical presentation of postoperative hyponatremic encephalopathy is neurogenic pulmonary edema,[26] now referred to as Ayus-Arieff syndrome.[27] Females,[6] children,[4] and patients with hypoxemia[28] or underlying CNS disease[19,29] are at highest risk for developing hyponatremic encephalopathy, and in these groups of patients, it can develop even at mildly hyponatremic values.

It is our opinion that any patient suspected of having hyponatremic encephalopathy, even if only mildly symptomatic, should be treated with a 2 mL/kg bolus of

3% NaCl or with a minimum of 100 mL, before proceeding with radiologic investigations.[10,30,31] Each bolus will result in at most a 2 mEq/L increase in serum sodium. The bolus can be repeated 2 to 3 times as necessary. This will result in an acute increase in serum sodium of 4 to 6 mEq/L, which will rapidly decrease brain edema and should result in clinical improvement. A patient who does not respond to this therapy likely does not have hyponatremic encephalopathy. No harm could come from this approach, because this degree of correction falls safely within even the most conservative recommendations for correction.[32] It must be emphasized that postoperative patients are at low risk for developing cerebral demyelination because this is an acute form of hyponatremia that is unlikely to overcorrect with therapy due to AVP excess.[7]

Based on all available data, there can be no justification for administering hypotonic fluids in the perioperative setting. It is clear that hypotonic fluids produce a postoperative decrease in serum sodium, from which fatal hyponatremic encephalopathy can follow. Significantly hypotonic solutions such as 5% dextrose in water or 0.2% and 0.45% NaCl should rarely if ever be used in the first 24 to 48 hours after surgery. Near-isotonic fluids such as lactated Ringer solution would best be avoided, and, if used, serum sodium should be monitored. Standardizing postoperative fluid therapy by using 0.9% NaCl could safely eliminate the complication of hyponatremic encephalopathy.

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